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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/711,101
Filing Date: August 23, 2004
Appellant(s): BLANCK ET AL.

Thomas Toner
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 26, 2007 appealing from the
Office action mailed December 13, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 9 and 11-13. Claim 10 is withdrawn from consideration as not directed to the elected invention.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The written description rejection as it applies to claims 12 and 13 is withdrawn.

(7) Claims Appendix

A substantially correct copy of appealed claims appears on page 16 of the Appendix to the appellant's brief. The minor errors are as follows: this listing contains claim 10 as being rejected and under appeal. This claim is withdrawn from consideration and is not under examination.

(8) Evidence Relied Upon

Opalinska et al. (Nature Reviews Drug Discovery 2002, vol. 1, pages 503-514)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Claims 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are directed to a method of treating a tumor in a subject by administering to the subject a therapeutically effective amount of an Oct-1 inhibitor. In a specific embodiment Oct-1 mRNA function is inhibited.

The claims encompass the use of inhibitors of Oct-1 of any type for the purpose of treating tumors. Inhibitors encompassed by the instant claims include nucleic acid-based inhibitors such as antisense oligonucleotides, ribozyme and siRNAs and also include non-nucleic acid inhibitors such as proteins, antibodies, small organic molecules and inorganic molecules.

The specification describes the administration of antisense sequences to Oct-1 for the purpose of western blotting. The specification further describes inhibition of Oct-1 expression using vectors encoding a full-length Oct-1 antisense sequence. Two of the transformants were shown to decrease cell growth as compared to a control vector. The structure of the Oct-1 antisense sequences are not disclosed, nor is the species of Oct-1 used disclosed, it is presumed to be human.

The specification discloses that a full-length antisense oligonucleotide inhibits Oct-1, however, antisense inhibitors are not a representative sample of Oct-1 inhibitors encompassed by the instant claims. While the skilled artisan requires only the sequence of a gene in order to easily produce nucleic acid-based inhibitors such as antisense oligonucleotides, non-nucleic acid inhibitors are not based solely on knowledge of a gene sequence and therefore cannot be produced so easily. The structure of a small molecule inhibitor of Oct-1 cannot be derived from the structure of a gene or even from the structure of the protein. The prior art describes two inhibitors of Oct-1, the polysaccharide heparan sulfate and the glycoprotein interferon- α but these substances are not representative of the inhibitors encompassed by the instant claims because the structures of these inhibitors do not lead the skilled artisan to envision the structure of other inhibitors that have the function of inhibiting Oct-1. The prior art does not describe Oct-1 inhibitors that are small organic or inorganic molecules.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

"An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did

not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.").

Neither the specification nor the prior art describe structures that are representative of the full genus of encompassed compounds that have the function of inhibiting Oct-1 and providing tumor treatment. The skilled artisan cannot envision the detailed structure of the encompassed modulating agents that inhibit Oct-1 mRNA function and decrease tumor growth, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claims 9 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a tumor in a subject by administering to the subject a therapeutically effective amount of an Oct-1 inhibitor. In a specific embodiment Oct-1 mRNA function is inhibited. The inhibitor can be a vector that contains an Oct-1 antisense sequence or can be an RNA inhibitor molecule.

The specification describes western blotting experiments wherein the amount of Oct-1 was quantified after treatment of a human bladder cancer cell line with vectors encoding a full-length antisense sequence. Two of the transformants decreased cell growth as compared to a control vector. The specification does not provide any examples where the antisense sequence are delivered to an organism, nor does the specification describe that inhibition of Oct-1 mRNA function led to the modulation of tumor growth in any organism.

Problems related to *in vivo* use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a significant or therapeutic effect.

Opalinska et al. state on page 511

"[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

"Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a

resultant treatment of tumors by inhibition of Oct-1 mRNA function, as claimed. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given the teachings of the prior art, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teaching of the prior art does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for inhibition of Oct-1 mRNA in cells *in vitro*, the specification is not enabling for the broad claims of treating tumors in a subject by inhibiting the expression of Oct-1 in any organism as the art of inhibiting gene expression by introducing oligonucleotides into an organism is neither routine nor predictable. The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in

scope with the claims without undue, trial and error experimentation and therefore, claims 9 and 11-13 are not enabled.

(10) Response to Argument

Appellants argue with regard to the written description rejection that the examiner does not dispute the existence of numerous other Oct-1 inhibitors, however it is noted that only two Oct-1 inhibitors are known from the art: heparan sulfate, a polysaccharide, and the glycoprotein interferon- α . Neither of these Oct-1 inhibitors is recognized to treat tumors by inhibition of Oct-1 and, even if these inhibitors did provide this function, these inhibitors are not representative of the genus of Oct-1 inhibitors because knowledge of the structure of these inhibitors will not lead the skilled artisan to the structure of other Oct-1 inhibitors.

Appellants further argue the absence of a working example is not fatal to compliance with the written description requirement where the specification otherwise conveys to one skilled in the art that the applicant's possessed the claimed invention at the time of filing. Appellants cite *Regents of the Univ. of Cal. v. Eli Lilly & Co* to note that genus claims are sufficiently enabled so long as one of ordinary skill in the art can "visualize or recognize the identity of the members of the genus" from reading the specification and assert that the mere fact that the specification fails to describe the full genus of encompassed compounds that have the function of inhibiting Oct-1 does not mean that the application fails to meet the written description requirement.

The examiner disagrees with this assertion, the fact that the specification fails to describe a representative sample of the full genus of encompassed compounds is precisely why the application fails to meet the written description requirement. The claimed method is directed to use of inhibitor of Oct-1 of any type in order to treat tumors in a subject. The specification describes antisense oligonucleotides targeted to Oct-1 and the prior art describes two inhibitors of Oct-1, a protein and a polysaccharide.

While the specification discloses one type of Oct-1 inhibitor and states at paragraph 32 that other modes of inhibiting Oct-1 protein or DNA-binding capacity can be practiced by one of skill in the art, based on the existence of antisense oligonucleotides, a polysaccharide and a glycoprotein, the skilled artisan would not be able to "visualize or recognize the identity of the members of the genus". The structures of interferon- α or heparan sulfate do not lead the skilled artisan to immediately visualize other proteins or polysaccharides that have the claimed function of treating tumors by inhibiting Oct-1. Similarly, these known inhibitors would not lead the skilled artisan to immediately visualize the members of the genus of Oct-1 inhibitors that are small molecules. Without disclosure of a representative sample of the species encompassed by the genus, the instant application does not satisfy the written description requirement.

With regard to the enablement rejection, appellants note that enablement of a genus under § 112, ¶ 1 can be established by showing enablement of a representative number of species within the genus. Appellants argue that

precise detail about the structural and chemical properties of the Oct-1 mechanism has been set forth and that inhibitors of Oct-1 are detailed by their functional characteristics coupled with the known correlation between Oct-1 function and structure. Appellants additionally argue the specification discloses the construction of a vector comprising antisense Oct-1 cDNA which can be used to inhibit Oct-1 expression and discusses screening assays which can be used for identifying such inhibitors. Appellants further argue that such screening assays, once identified, can be routinely used by those of ordinary skill in the art to screen compounds for similar activity and conclude that because the Office has advanced no specific reasoning why the compound screening assays outlined in the specification would be unsuccessful in identifying other similar agents, there is not sufficient evidence to support a finding of lack of enablement of the claimed invention. Appellants further argue that methods of modulating gene expression, both *in vitro* and *in vivo*, were well known prior to Applicant's filing date and note that methods to identify the necessary characteristics, including affinity, of expression modulators, such as those used in the invention were known in the art at the time the application was filed.

Appellants' arguments are based on the proposition that the written description requirement is satisfied because the Oct-1 inhibitors encompassed by the claimed invention can be found by performing a screening assay and that the claims are therefore enabled. The specification does contemplate at paragraph 11 that the invention provides an assay for testing anti-cancer therapeutics and states at paragraph 32 that other modes of inhibiting Oct-1 protein or DNA-

binding capacity can be practiced by one of skill in the art. However, it is well established that disclosure of an assay for identifying compounds useful in a method is not sufficient to satisfy the written description requirement. For example, MPEP 2163 states in part,

"An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.").

Appellants additionally argue that the references cited by the Examiner show that Oct-1 inhibiting substances are sufficiently well known in the art such that one could routinely apply Applicant's techniques to inhibit Oct-1 without undue experimentation. As noted in response to appellants' arguments regarding the written description rejection, the known inhibitors of Oct-1, heparan sulfate and interferon- α , are not representative of the claimed genus of inhibitors because the structure of these inhibitors does not allow the skilled artisan to immediately visualize other inhibitors of Oct-1.

With regard to the grounds of rejection directed to unpredictability of *in vivo* administration of nucleic acid therapeutics, appellants argue the examiner is applying a *per se* rule, apparently because the passage quoted from Opalinska et al. contains the phrase "as a general rule". This reference is cited to provide reasons why those in the art of nucleic acid therapeutics recognize that specific

issues with regard to delivery of nucleic acids *in vivo* render the art unpredictable.

The mere presence of the phrase "as a general rule" in the reference is not intended to indicate that the rejection itself is based on a *per se* rule.

Appellants argue that methods of modulating gene expression were well known prior to the filing date, citing two patents containing claims to such methods. It is correct that methods of modulating gene expression were known in the art; however, the cited patents appear to be directed to the use of small molecule chemical modulators (as evidenced by the working examples) and do not provide evidence that delivery of nucleic acid therapeutics *in vivo* is predictable. Also, the instant claims are not directed to a method that has as final outcome modulation of gene expression, but to a method of therapy by treatment of tumors.

Appellants additionally argue the specification of the application and the references highlighted by the Office show that the modulation of Oct-1 was known in the art. This argument is directed to the references cited by the examiner that describe heparan sulfate and interferon- α as Oct-1 inhibitors, but it is noted that these inhibitors are not nucleic acids and therefore do not address the specific grounds of rejection that are based on the art recognized unpredictability of delivering nucleic acid therapeutics *in vivo*. Additionally, modulation of Oct-1 for the purpose of treating tumors was not known prior to the instant application, therefore use of Oct-1 inhibitors described in the prior art cannot be relied upon to demonstrate enablement of the instant claims for therapeutic purposes.

Appellants argue the 5637 cell line used in the examples correlates to the breadth of the claims, noting that this cell line is recognized in the ATCC CULTURES TM cell line list as a tumor cell line and citing the Muthing reference as an example where the 5637 cell line was selected as representing malignant cells of epithelial morphology. Based on these arguments, appellants assert that the specification clearly shows the requisite correlation of the prophetic example to the claimed activity since the 5637 cell line possesses "increased Oct-1 binding activity" and that "Oct-1 is hypophosphorylated in 5637 cells, which subsequently increases its DNA binding activity" and have a "high level of active Oct-1 as compared to non-cancerous cells."

This argument appears to be that the cell line used in the working example of the specification is a model for cancer. The basis of the rejection, however, is not whether the cell line used in the example is an acceptable model for cancer, but that the delivery of nucleic acid inhibitors is recognized in the art as unpredictable. However, this argument is also not persuasive because the characteristics of the cell line cited by appellants are not required when performing claimed method, which is directed to treatment of tumors generally, not only those characterized by having increased binding activity of Oct-1 or hypophosphorylation of Oct-1.

Appellants further argue the claims do not require a therapeutic response, noting that the sole active step is administration of an Oct-1 inhibitor and the examiner has not stated that the term "therapeutically effective amount" is not enabled. This argument is not persuasive because the claims do require a

therapeutic response, being specifically directed to treatment of tumors in subjects in need thereof. It is correct that the term "therapeutically effective amount" has not been specifically rejected because if the claimed method is enabled, determining the proper dosage would be a matter of routine experimentation.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Tracy Vivlemore



Conferees:

James Schultz



J. DOUGLAS SCHULTZ, PH.D.
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Joseph Weitach



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